A microtubule based control mechanism for perception-action behavior in a simulated eukaryotic cell.

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Eukaryotic cells are capable of performing very complex information processing tasks, and can be thought of as a computational device capable of performing perception-action behavior. This behavior takes the form of the cell extracting information from the local environment, integrating the information relative to the current internal state, and producing an action to enhance the cell's fitness in the current environment. To facilitate this sort of information processing the cell would need to work in a coordinated fashion requiring a long-range signaling mechanism that can integrate information from across the cell quickly. Many short-range signaling mechanisms have been identified in the eukaryotic cell biology, but a long-range signaling mechanism has yet to be conclusively established. However, evidence indicates that the cytoskeleton could fill this long-range signaling role, specifically the microtubule network because of its organizational characteristics.

To explore this proposed signaling medium a learning model is used that combines a biologically motivated growth simulation with an abstract signaling mechanism to create an adaptive signaling medium. This signaling medium is molded by *adaptive self-stabilization* [1], which is essentially a feedback mechanism that translates network fitness into regulatory signals for modulating the growth dynamics. Ultimately a goal of this work is to harness the model's inherent oscillatory dynamics for controlling a biomimetic robot that captures the interdependent nature of the eukaryotic cell's various components.

The microtubule network is one of three components that make up the eukaryotic cell's cytoskeleton, playing the role of gross structural support and organizer of intracellular organelles. What sets the microtubule network apart from the other cytoskeletal components is its unique organization, which makes the network especially useful for efficient transport of proteins throughout the cell interior and potentially providing an effective long-range signaling medium. Microtubule networks consist of three basic components: microtubules, the Microtubule Organizing Center (MTOC), and Microtubule-Associated Proteins (MAPs). The microtubules themselves are large macromolecular tube-like structures composed of tubulin dimers that assemble by a growth mechanism called *dynamic instability* [2]. This growth mechanism produces a system where individual microtubules stochastically oscillate between assembly and disassembly, while the larger microtubule population maintains a stable net mass of assembled structure. The MTOC is a protein matrix around the cell's centrosome, which nucleates new microtubules while providing orientation to existing microtubules so that they radiate from the cell center to the outer cell periphery. MAPs are a large family of proteins that are capable of binding to the microtubules and allow the network to generate cell specific functionality. MAPs provide a variety of functions, including: stabilizing assembling microtubules, linking microtubules to other intracellular components, facilitating protein transport, and providing micro-muscle activity.

Several researchers have implicated the cytoskeleton as a mechanism for long-range signaling in the cell, specifically the microtubule network, because of its regular organization that reaches from the cell center to the periphery. Evidence for these interconnections have been shown to exist, whereby mechanical signals can be transmitted from the cell surface to the nucleus [3]. These interconnections start with proteins called integrins in the outer (plasma) membrane that are bound to the underlying cytoskeletal substructure, which in turn connects to the nuclear structure and allows a tug on the integrins to be transmitted to the cell nucleus. It was this interconnection and evidence for a long range signaling mechanism in the neuron that lead to the suggestion that the cytoskeleton, and specifically the microtubule network, is the neuron's "micro-nervous system". This resulted in a variety proposed signaling models in the literature [4], the majority of which are based on a type of vibratory dynamic.

Our learning model consists of three phases: growth, signal processing, and adaptive self-stabilization. During the growth phase, the microtubule network is allowed to develop in a three dimensional array of cubes that abstracts the intracellular environment and preserves the spatial arrangement found in the natural system (see Figure 3.1). The developed network is then reinterpreted by the signal-processing phase, which treats individual microtubules as strings of discrete oscillators that are interlinked by bound MAPs capable of actively modulating the signaling effects. Adaptive self-stabilization modifies the growth dynamics based on the fitness, which is derived from the network's signal processing capability. This fitness-based signal has the effect of stabilizing the microtubule network over time as the fitness value increases.

The behavior of the learning model is to begin with no microtubule network structure, which provides zero fitness since there is no network to support an information transform. Microtubule network structure will quickly begin to build up, although at this point the signaling pathways are incomplete and will provide a very low fitness. At some point a critical amount of network structure will be generated to support an effective set of signaling pathways, which will increase fitness and lead to a progressively more stable structure. This development of effective signaling pathways can be seen in experimental results presented in Figure 3.2.

The task given to the model for these results was to find the center point in a two-dimensional array from a random position. The learning model does this by taking the current location as input, integrating the information relative the current network dynamics, and producing an offset relative to the current array position for the next position. The process is then repeated with the new array position without resetting the internal network dynamics, providing a rough perception-action framework for the model to function within. In Figure 3.2 each rectangle shows the learning model's ability to perform the task for eight randomly generated points, with each arrow indicating direction and distance offset. At time points 10 through 54, little movement occurs beyond the initial random location generated and is due to the initial lack of developed network structure. However, as time progresses structure begins to develop that allows the model to begin producing useful effects and will eventually stabilize into more useful configurations (see time periods 211 and 562). It should be noted that the problem was partially encoded into the MAP functionality, allowing the learning model to achieve a "sense of direction" in the 2-dimensional array that can then be regulated by the correct placement of MAP on the microtubule network. Eventually this encoding will be replaced by an evolutionary

mechanism that evolves different MAPs types, eliminating the need for this kind of direct control over the model.

The learning model's signaling mechanism treats each microtubule as a string of simple discrete oscillators with neighbor-neighbor interactions. The reason for this representation is that a variety of possible vibratory dynamics can be represented in an abstract way; a second advantage of this implementation is that it provides a computationally simple simulation. MAPs are used in the signal processing mechanism to introduce active effects to the otherwise passive microtubule substrate, much the way MAPs interact with microtubules in the natural system. In the case of the learning model, MAPs: introduce signals into the microtubule network, exchange signals between neighboring microtubules, and extracts signals from the structure. As a result of this microtubule-MAP interaction MAPs produce a periodic triggering activity that mirrors the underlying microtubule network dynamics, producing behavior that is reminiscent of a spike train generated by a neuronal action potential.

To expand upon this simulation of information processing in the eukaryotic cell, the learning model will ultimately will be integrated with a biomimetic robot that abstracts eukaryotic cell functionality. The robot, called biot, consists of a sequence of twelve segments that are interconnected with both local and distant neighbor segments in a non-regular fashion to promote context sensitive interactions between the different segments. As a result of these complex interactions the current shape of biot cannot be calculated based on previous movements, instead a set of optical sensors are positioned throughout the device to provide a general feedback mechanism about the robot's shape. The resulting interactions between each segment produces movements similar to a biological system that when combined with the general feedback mechanism provides a very natural representation of a biological system.

The month spent at NASA-Ames Research Center focused on integrating the microtubule based learning model within the context of this perception-action framework of the eukaryotic cell. Additional work also examined various options of how to utilize the oscillatory dynamics inherent to the learning model so as to be an effective control mechanism for the biomimetic robot. This research avenue was followed for two reasons: first, the learning model functions well in a perception-action framework that would be required for manipulating the complex interactions needed to control the biot; second, the adaptive nature of the learning model would allow the biot to respond to changes in the local environment like encountering new terrain features. Additionally, by combining this learning model with the biot it would provide an abstraction for the exploration of the eukaryotic cell and how it coordinates the diverse intracellular activities to produce clear cohesive actions towards a goal that the cell perceives as necessary, usually resulting in a higher fitness and thus a better chance for continued survival.

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Figure 3.1- an example of the first 10 time steps of a developing microtubule population. Single black cubes represent new microtubules, while older microtubules are a black cube paired with a white rectangular cube. At time 0 the simulated cellspace is empty, at time 1 14 new microtubules are created, at time 2 10 of the 14 microtubules grow one array location, and so on.

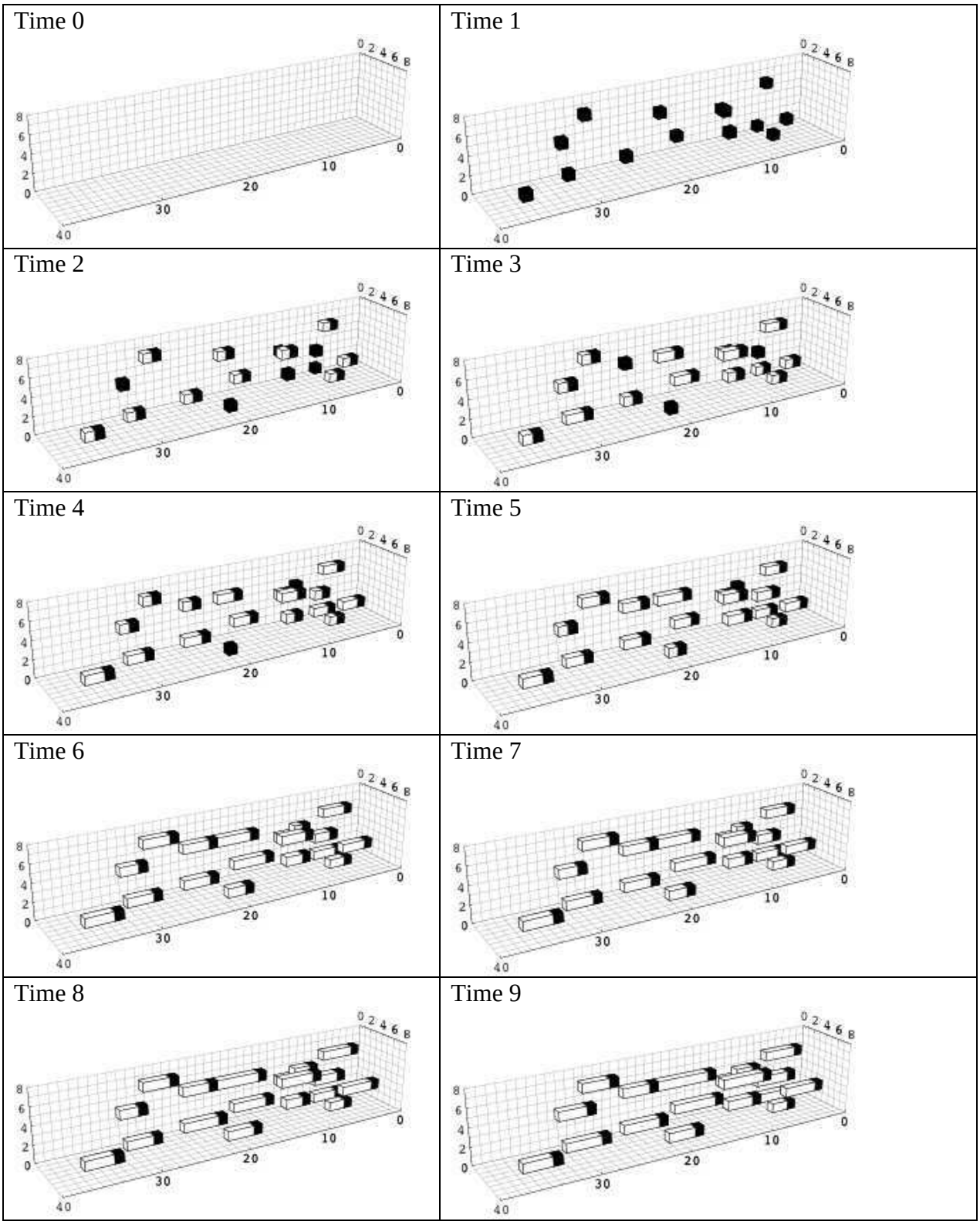

Figure 3.2 – experimental results where the learning model was given a random position in the 2-dimensional array and required to find the middle position. A black cross indicates the center and each start position is given as a black dot. The model's movement is given as a sequence of blue lines with an arrow to indicate direction and distanced moved. Fitness is determined based on the distance to the center, relative to the starting distance.